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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/750,410	12/28/2000	Gloria C. Li	55672-A-PCT-US/ JPW/AJM/M	6916

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM

Office Action Summary	Application No.	Applicant(s)	
	09/750,410	LI ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3-8-04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 18-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6-4-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 3-8-04.

Claims 1-16, 18-24 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 18-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "linked to a regulatory element" in claim 18, lines 1 and 2, is vague and unclear as to how or with respect to what orientation the antisense is linked to a regulatory subunit (e.g. inserting—operably—before "linked" would be remedial). Appropriate clarification is requested.

Claims 1-16, 18-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the reasons of record set forth in the Office action mailed 11-18-03.

Applicant's arguments filed 3-8-04 have been fully considered but they are not persuasive. Applicants argue that the instant invention satisfies the written description requirement, adequately describing the broad genus comprising antisense

oligonucleotides that specifically hybridize to any nucleic acid encoding a DNA-dependent protein kinase subunit because the DNA-dependent protein kinase catalytic subunit, Ku70 and Ku80 are parts of a protein complex that is well documented in the art, and which has been described on page 1, line 31-page, line 1 of the instant specification. Contrary to Applicants' assertions, the genus comprising antisense oligonucleotides that specifically hybridize to any nucleic acid encoding a DNA-dependent protein kinase subunit encompasses a myriad of nucleotide sequences, and a representative number of species for this broad genus has not been provided in the instant disclosure. The specification generally describes the claimed genus as antisense that specifically hybridize to any of three subunits, Ku70, Ku80 or the catalytic subunit, of the serine/threonine kinase DNA-dependent protein kinase. The nucleotide sequences encoding each of these three subunits have been described in the instant disclosure and in the prior art for both mouse and humans (e.g. see pages 1, 2, 24, 4346 of the instant specification. And the DNA-dependent protein kinase has been identified in mouse and humans as being responsible for DNA strand repair. In addition, null mutants or knockouts of the Ku70 and/or 80 subunits have been characterized extensively in mice. The claimed genus, however, encompasses any antisense oligonucleotides capable of specifically hybridizing to the nucleotides encoding the corresponding subunits of the kinase from <u>any</u> species, and is not limited to mouse and humans. The genus comprising antisense <u>complementary</u> to the three subunits, Ku70, Ku80 or the catalytic subunit, of the human and mouse serine/threonine kinase DNA-dependent protein kinases has been adequately in the instant specification and in the

art. But the genus comprising antisense specifically hybridizing to the three subunits, Ku70, Ku80 or the catalytic subunit, of the human and mouse serine/threonine kinase DNA-dependent protein kinases is very broad and reads on a myriad of nucleotide sequences that are not adequately described in the instant specification or art. Similarly the genus comprising antisense complementary to or specifically hybridizing to the three subunits, Ku70, Ku80 or the catalytic subunit, of serine/threonine kinase DNA-dependent protein kinase from other species (e.g. not mouse or human) has not been adequately described in the instant specification or prior art.

Adequate written description has been provided for antisense complementary to the three subunits, Ku70, Ku80 or the catalytic subunit, of the previously characterized mouse and human DNA-dependent kinase – all of known nucleotide sequences. But this does not provide adequate written description for the broad genus claimed, comprising any antisense complementary to Ku70, Ku80 or the catalytic subunit, of any DNA-dependent kinase. Therefore, the rejection is maintained.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions and methods for increasing the susceptibility of a cell to DNA-damaging agents comprising the in vitro administration of an antisense oligonucleotide that is complementary to and inhibits the expression of a nucleic acid encoding a subunit of mouse or human DNA dependent protein kinase (DNA-PK) of previously known nucleotide sequence, does not reasonably provide enablement for increasing the susceptibility of a cell to DNA-damaging agents in vivo, or

to treat any tumor or any cancer in a subject, comprising the administration of an antisense oligonucleotide that specifically targets and inhibits the expression of any nucleic acid encoding any subunit of DNA dependent protein kinase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the reasons of record set forth in the Office action mailed 11-18-03.

Applicant's arguments filed 3-8-04 have been fully considered but they are not persuasive. Applicants argue that enablement has been satisfied in the instant application because the specification teaches that cells deficient in DNA-PK subunits have an increased sensitivity to radiation induced apoptosis. This has been illustrated in the instant disclosure by showing Ku70-deficient fibroblasts from Ku70 deficient mice having increased radiosensitivity in vitro and in vivo. But it is not contested that increased radiosensitivity occurs is cells lacking functional DNA-PK subunits, as illustrated in the instant disclosure. But this is not the claimed invention. The instant invention claims metods of increasing cell susceptibility to DNA damaging agents and methods of treating cancer requiring the successful targeting, delivery and inhibition of DNA-PK using antisense in vivo. The instant rejection, therefore, is based on the unpredictability of successfully targeting and inhibiting the expression of the target DNA-PK subunit molecules by administering antisense in vivo and providing for the secondary effect of increasing the susceptibility of a cell to a DNA-damaging agent. This is the basis of unpredictability in the art that triggers the instant rejection for lacking enablement over the scope claimed. The instant invention is enabled for increasing

radiosensitivity in cells in vitro and vivo in previously generated DNA-PK subunit deficient mice, as illustrated in the instant disclosure But the ability to successfully target and inhibit expression of the target DNA-PK in vivo using antisense requires experimentation beyond that provided in the instant disclosure. Null mutants or knockouts of a target gene of interest do not substitute for the ability to successfully target and inhibit the expression of a gene in vivo using antisense. And one cannot extrapolate the success obtained using antisense for one target gene in vivo for that of another and unrelated target gene. As indicated by Crooke and Branch in the prior Office action mailed 11-18-03, antisense inhibition in vivo is a highly unpredictable endeavor due to target accessibility and delivery issues, and cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The ability to inhibit expression of a target gene in vivo using antisense will depend on the accessibility of that target gene for antisense binding, as well as the accessibility of the target cells harboring that target gene, and the route of antisense administration utilized (e.g. systemic or direct administration...). Applicants are also directed to the teachings of Agrawal (cited in the Office action mailed 11-18-03), that state that non-antisense effects attributed to secondary structure and charge, as well as biological effects exerted by sequence motifs existing within the antisense sequences, provide for unpredictable in vivo side effects and limited efficacy (e.g. see pages 72-76 of Agrawal, also on page 80: "It is therefore appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide."). In addition, the cellular uptake of

antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327). Therefore, the instant rejection for lacking enablement over the scope claimed is maintained.

New Rejections and Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Takiguchi et al.

Takiguchi et al (Genomics 35: 129-135, 1996) teach antisense oligonucleotides that specifically hybridize and inhibit expression of a DNA-PK subunit (see page 130, last paragraph on the left, first paragraph on the right).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 15,16 and 18-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takiguchi et al as applied to claim 15 above, and further in view of Au-Young et al (USPN 5,773,580).

The claims are drawn to compositions and methods for increasing a target cell's sensitivity to DNA damaging agents comprising the in vitro administration of antisense oligonucleotides (and ribozymes) specifically targeting a nucleic acid encoding a DNA dependent protein kinase subunit, which antisense inhibit the expression of the target DNA PK catalytic or Ku70 subunit, and which antisense are in an appropriate expression vector, operably linked to a heat shock promoter, and optionally linked to a ribozyme.

Takiguchi et al (Genomics 35: 129-135, 1996) teach antisense oligonucleotides that specifically hybridize and inhibit expression of a DNA-PK subunit (see page 130, last paragraph on the left, first paragraph on the right). Taniguchi et al also teach the role of DNA-PK in DNA repair, and an increase in a cell's sensitivity to DNA damaging agents with loss of DNA-PK function (see page 129, right col).

Takiguchi et al do not teach vectors or pharmaceutical compositions comprising antisense or ribozymes, nor vectors comprising inducible promoters such as the heat shock promoter.

Au-Young et al teach pharmaceutical compositions comprising antisense oligonucleotides for inhibiting a known target gene, as well as teaching expression vectors comprising antisense oligonucleotides and ribozymes, which oligonucleotides are operably linked to regulatory elements including an inducible (heat shock) promoter (see esp. col. 10-11, 20-21).

It would have been obvious to one of ordinary skill in the art to insert antisense oligonucleotides into an appropriate expression vector, operably linked to an inducible promoter including a heat shock promoter, because such expression systems have been used routinely in the art for expression of nucleic acid constructs including antisense and ribozymes in an appropriate target cell, as taught previously by Au-Young et al. One of ordinary skill in the art would have been motivated to operably link an antisense oligonucleotide to an inducible promoter in an appropriate expression vector in order to control the conditions of expression of the operably linked antisense, and in order to control conditions for antisense expression and subsequent inhibition of the antisense's target gene in an appropriate target cell. One of ordinary skill in the art would have been motivated to target and inhibit the expression of DNA-PK in order to increase a target cell's sensitivity to DNA damaging agents (e.g. a target cancer cell), because Taniguchi et al teach the relationship between increasing cell radiosensitivity or loss of DNA repair function, and loss of functional DNA-PK. One of ordinary skill in

the art would have expected that by utilizing appropriate conditions for expression (e.g. induction by heat), the antisense targeting DNA-PK would be expressed upon induction of the heat shock promoter because such induction systems as heat shock promoters have been routinely used as described by Au-Young et al. One of ordinary skill in the art would have been motivated to induce expression of antisense and ribozymes under desired conditions (e.g. upon exposure heat) because induction is a way of controlling the conditions for increased expression of the operably linked antisense and ribozymes, and also a way of controlling the subsequent inhibition of target gene expression following expression of these antisense. In this way, increasing a cell's sensitivity to DNA damaging agents is in turn induced following heat treatment and expression of antisense. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-16, 18-24 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-24 of copending Application No. 10/712,642. This is

a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ
5-25-04

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